

### **REMARKS**

Claim 9 is pending in the application. Claim 9 has been amended to specify that the non-natural pyrimidine nucleoside is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil. Support for this amendment is found in the specification as filed at page 13, lines 6-8. No new matter has been added. Claims 11 and 39 have been canceled. Each presently maintained rejection of claim 9 is separately addressed below.

#### **Rejection of Claim 9 Under 35 U.S.C. §103(a): Schwartz/Peyrottes**

Claim 9 is rejected under 35 U.S.C. §103(a) as being unpatentable over Schwartz et al. as evidenced by Peyrottes et al.

Claim 9 has been amended to specify that the non-natural pyrimidine nucleoside is selected from 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil. Neither Schwartz nor Peyrottes teaches or suggests such a replacement for cytosine in a CpG dinucleotide of an immunostimulatory oligonucleotide. Accordingly, Applicants respectfully request that this rejection be withdrawn.

#### **Rejection of Claim 9 Under 35 U.S.C. §103(a): Nguyen in view of Schwartz**

Claims 9 is rejected as being obvious over Nguyen et al in view of Schwartz et al. Applicants respectfully disagree. This rejection fails for two reasons. First, Nguyen is non-analogous art, and as such, is improper to be relied upon in an obviousness rejection. Second, the rejection relies upon legal error regarding the application of allegedly inherent properties of a reference in an obviousness rejection.

To be cited in an obviousness rejection, a reference must meet one of two standards. It must either be in Applicants' field of endeavor, or it must be pertinent to the problem that Applicants sought to solve. Nguyen meets neither of these standards.

As to field of endeavor, Nguyen relates to the field of DNA sequencing by hybridization. Applicants' field of endeavor is immunology, specifically the use of modified, oligonucleotide-based compounds to elicit an immune response. One skilled in Applicants' field would not look to the DNA sequencing art to apply it to Applicants' field. Thus, Nguyen fails the first prong of the test.

Second, Nguyen is not pertinent to the problem that Applicants sought to address. Applicants sought to discover new immunostimulatory motifs that would be effective in inducing an immune response in an immunostimulatory oligonucleotide. Nguyen sought to smooth the thermal stability of DNA duplexes independent of their base composition for DNA sequencing by hybridization. Thermostability of a DNA duplex is irrelevant to Applicants' problem. Applicants' problem deals with an oligonucleotide-based compound that produces a phenomenon that occurs within the body of a living organism. Nguyen has nothing to do with any effect of an oligonucleotide within the body of a living organism. Thus, it is clear that Nguyen is not pertinent to the problem that Applicants sought to address. For this reason alone, this rejection should be withdrawn.

In addition, the rejection continues to rely on reversible legal error as to the treatment of allegedly inherent properties of a compound in an obviousness rejection. In fact, the rejection fails to consider the case law submitted in Applicants' previously filed reply. Neither *Kloster Speedsteel* nor *Dillon* is even mentioned in the present rejection. The rejection relies upon *Atlas Powder* for the proposition that "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer". (page 9, emphasis added) Applicants do not dispute this. However, this proposition applies to novelty. The correct standard for evaluating allegedly inherent features of a prior art compound in an obviousness analysis that combines references is whether the inherency of the feature was itself known or obvious at the Applicants' filing date. This legal standard is ignored in the presently maintained rejection. Since the case law submitted by Applicants has not been addressed in the rejection, that law is again brought to the PTO's attention.

*Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565 (Fed. Cir. 1986) is on point and is quoted here.

Stora bases a major argument on the undisputed fact that size change uniformity is an inherent property of the alloy disclosed in the '518 patent. That argument is unpersuasive when confronted by Stora's failure to establish at trial that that inherency would have been obvious to those skilled in the art when the invention of claim 4 was made. Inherency and obviousness are distinct concepts. *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1555, 220 USPQ 303, 314 (Fed. Cir. 1983) (citing *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (1966)), *cert. denied*, 469 U.S. 851, 105 S.Ct. 172, 83 L. Ed.2d 107 (1984). (emphasis added)

*In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990) is also on point, stating that:

The board stated that it is inherent in Dillon's compositions that they would reduce particulate emissions, that Dillon "merely recited a newly discovered function inherently possessed" by the prior art. Arguments based on "inherent" properties can not stand when there is no supporting teaching in the prior art. Inherency and obviousness are distinct concepts. In *re Spormann*, 363 F.2d 444,448, 53 CCPA 1375, 150 USPQ 449, 452 (CCPA 1966):

[T]he inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. (emphasis added)

Nguyen does teach, in an entirely different context, oligonucleotides in which one or more C is replaced by N4-ethylcytosine. However, it was not known at Applicants' filing date that such a modified C would be immunostimulatory in a CpG dinucleotide of an immunostimulatory oligonucleotide. This is directly on point with *Dillon's* admonition that "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."

The rejection attempts to salvage its' position by stating that "The oligonucleotide of Nguyen et al. inherently has immunostimulatory activity, for at the time of Applicant's filing date, Schwartz et al. evidences that the presence of a CpG motif in an oligonucleotide renders the oligonucleotide immunostimulatory." (page 7, emphasis added) This completely dismisses Applicants' invention. Yes, Schwartz, among other references prior to Applicants' filing date, teaches that a CpG motif is immunostimulatory. However, neither Schwartz, nor any other reference of record, suggests that an N4-ethylCpG motif is immunostimulatory. Thus, Schwartz does not salvage the rejection. It is clear from the record that even if a N4-ethylCpG motif in an oligonucleotide disclosed in Nguyen was inherently immunostimulatory, that inherent feature was not known as of Applicants' filing date. Thus, just as in *Dillon*, in the present case obviousness cannot be predicated on what is unknown.

Not only is this the law on the matter, it is also common sense. If nobody knew that the N4-ethylCpG motif of Nguyen was immunostimulatory, why would one of ordinary skill in the art even consider substituting it into Schwartz's oligonucleotide? Simply put, they wouldn't. Thus, it would not even be obvious to try such a substitution.

Accordingly, for this reason also, Applicants' respectfully request that this rejection be withdrawn.

Rejection of Claim 9 Under 35 U.S.C. §103(a): Zhao in view of Schwartz

Claims 9 is rejected as being obvious over Zhao et al in view of Schwartz et al. Neither Zhao nor Schwartz teaches or suggests the substitution of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine or 4-thiouracil for cytosine in a CpG dinucleotide of an immunostimulatory oligonucleotide. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejection of Claim 9 Under 35 U.S.C. §103(a): Agrawal in view of Schwartz

Claims 9 is rejected as being obvious over Agrawal et al in view of Schwartz et al. Neither Agrawal nor Schwartz teaches or suggests the substitution of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine or 4-thiouracil for cytosine in a CpG dinucleotide of an immunostimulatory oligonucleotide. Accordingly, Applicants respectfully request that this rejection be withdrawn.

**CONCLUSION**

In view of the above amendments and remarks, it is believed that claim 9 is in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner believes that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney at 781-933-6630.

Respectfully submitted,

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